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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/954,954 10/21/97 SUMMERS

N 2991/1

EXAMINER

HM12/1014

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ART UNIT

PAPER NUMBER

1646

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/954,954

Applicant(s)

Summers et al.

Examiner

Elizabeth C. Kemmerer

Group Art Unit

1646



☒ Responsive to communication(s) filed on 1 Sep 1999

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-22 is/are pending in the application.

Of the above, claim(s) 15-22 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-22 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment filed 01 September 1999 (Paper No. 12) has been entered in full. Claims 15-22 remain withdrawn from consideration as being directed to a non-elected invention. Claims 1-14 remain pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 11, 2, 5, 6 and 10-14 under 35 U.S.C. § 112, first paragraph, regarding new matter as set forth at pp. 2-3 of the previous Office Action (Paper No. 9, 29 April 1999) is *withdrawn* in view of the amended claims (Paper No. 12, 01 September 1999).

The rejection of claim 1 under 35 U.S.C. § 112, second paragraph, as set forth at p. 3 of the previous Office Action (Paper No. 9, 29 April 1999) is *withdrawn* in view of the amended claim (Paper No. 12, 01 September 1999).

35 U.S.C. § 112, Second Paragraph

Claims 4, 9 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

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the invention. The basis for this rejection is set forth at p. 3 of the previous Office Action (Paper No. 9, 29 April 1999).

Applicant argues (p. 5, Paper No. 12, 01 September 1999) that the amendment has overcome the rejection. This has been fully considered but is not found to be persuasive, because claim 4 still states that the polypeptide of SEQ ID NO: 123 is a linker of SEQ ID NOS: 124-130. A single sequence cannot be both. The Examiner's previous suggestion was abbreviated and therefore may have been confusing, which is regretted. The following is one way to resolve the issue: "The Erythropoietin receptor agonist polypeptide of claim 3 wherein the linker is selected from the group consisting of SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, and SEQ ID NO: 130."

35 U.S.C. § 103

Claims 1, 5 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin as set forth at pp. 3-8 of the previous Office Action (Paper No. 9, 29 April 1999).

Applicant's arguments (pp. 5-10, Paper No. 12, 01 September 1999) have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant cites *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ2d 1016), which ruled on the Lin et al. patent 4,703,008 applied in the instant rejection. Applicant points to the court's ruling that the '008 patent's specification does not provide enabling support for claims embracing biologically functional EPO gene analogs. Applicant concludes that '008 can only be relied upon for

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enabling the sequences of monkey and human EPO, but not analogs thereof such as amino acid sequences having substitutions at which murine and human EPO differ. Applicant urges that, specifically, '008 cannot be relied upon for teaching breakpoints at positions 25, 27, 30, 32, 80, 82, 88, 116, or 121 for circular permutation. This has been fully considered but is not found to be persuasive. First, the instant fact pattern is clearly distinguished from the fact pattern used in the *Amgen v. Chugai* decision. In *Amgen v. Chugai*, the court was determining enablement issues relevant to gene sequences, not amino acid sequences. Moreover, in the instant rejection, '008 is not relied upon for teaching *any* biologically functional analog. Rather, Pastan et al. (5,635,599) is being relied upon for teaching circular permutation of soluble ligands or growth factors, for suggesting EPO as such a growth factor (column 4, line 40), and for suggesting that non-conserved amino acid positions in an alignment of two closely related proteins are good candidates for opening sites (column 8, lines 45-53). '008 provides the alignment of two closely related EPO proteins, one from human and the other from monkey, and shows which amino acid residues are non-conserved. Following the disclosure of Pastan et al. ('599), these are good candidates for opening sites, and provide a reasonable expectation of success. Pastan et al. ('599) also teach how to confirm that these are good opening sites, by making the circular permuteins and testing for native activity. Therefore, the combined teachings suggest the claimed invention with a reasonable expectation of success.

Applicant also argues that the teachings of Pastan et al. ('599) are limited. Applicant urges that Pastan et al. ('599) only teaches two circular permuteins of IL-4 in the context of a chimeric molecule; only one circular permutein of each of IL-2, G-CSF and GM-CSF which were not

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demonstrated to have activity; and no working examples of EPO circular permuteins. Applicant also argues that the totality of the prior art provides only a limited number of examples of circular permuteins. Applicant asserts that Pastan et al. ('599) provides generic but unsupported speculation regarding breakpoints, although Applicant fails to provide any evidence regarding this point. Applicant next reviews the file history of Pastan et al. ('599) which was also examined by the instant Examiner. To summarize Applicant's review, Applicant stresses that the Pastan et al. claims were rejected for lack of enablement multiple times and implies that the Examiner then was persuaded to allow broad claims for circular permuteins of IL-4, IL-2, G-CSF and GM-CSF without adequate explanation on the record. Applicant concludes that Pastan et al. ('599) cannot be relied upon to teach circular permutation of any ligands other than a limited number of IL-4, IL-2, G-CSF and GM-CSF permuteins, and that it cannot be relied upon at all regarding EPO. Applicant characterizes Pastan et al. ('599) as an invitation to experiment, the teachings of which cannot be relied upon for suggestions of opening sites. This has been fully considered but is not found to be persuasive. First, it is important to recognize that, even though the instant Examiner is the same as that who examined the Pastan et al. ('599) patent, it would be wholly inappropriate for the Examiner to offer any information beyond that which is found in the official record of the prosecution history of the Pastan et al. ('599) patent. This is always true, but especially critical in the instant case, since the instant attorney, inventors and assignee are completely unrelated to those of the Pastan et al. ('599) patent. Thus, the prosecution history of the Pastan et al. ('599) patent must speak for itself. Broad claims were allowed, and they must be presumed valid unless *proven* otherwise. No such proof has been

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set forth. Second, it is important to realize that the Pastan et al. ('599) patent is the first to claim circular permuteins of any protein. It is clear from the Pastan et al. prosecution history and the prior art of the Pastan et al. record that it was highly unexpected that such a drastic change in the primary structure of any protein would result in an active variant. Therefore, Pastan et al. ('599) can and should be considered a pioneering patent. The suggestions Pastan et al. ('599) made regarding choice of opening site were shown to be valid with respect to the claimed IL-4, IL-2, G-CSF and GM-CSF permuteins. No evidence of the inaccuracy of these suggestions has been established. Finally, it is important to note that the instant claimed invention lists any of 67 potential breakpoints, not all of which have been exemplified in the specification. Surely, the claims embrace inoperative embodiments. However, this is legally permissible, since there would only be a reasonable number of inoperative embodiments, and the screening assay is disclosed such that the active permuteins could be easily identified by the skilled artisan. Thus, the combination of Pastan et al. and Lin et al. suggest the claimed invention with at least as reasonable of an expectation of success as the instant disclosure.

The rejection is deemed to be sound and is thus maintained.

Claims 1-4 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin and further in view of Chaudhary et al. as set forth at pp. 8-9 of the previous Office Action (Paper No. 9, 29 April 1999).

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Applicant's arguments (pp. 10-12, Paper No. 12, 01 September 1999) have been fully considered but are not deemed to be persuasive for the following reasons. As a preliminary matter, and in the interest of clarity, it is respectfully pointed out that Applicant mistakenly refers to patent 4,751,180 as Gearing et al. when in fact it is Cousens et al. Applicant argues that the arguments regarding Pastan et al. and Lin et al. are applicable in this rejection as well. This has been fully considered but is not found to be persuasive for the same reasons set forth above in the rebuttal of those arguments.

Applicant also argues that the linkers of Chaudhary et al. and Cousens et al. are in the context of fusion proteins and are used for different purposes, i.e., to provide sufficient space between the two fused proteins to allow for steric flexibility and proper folding. Applicant states that the instantly claimed linkers serve a different purpose, i.e., to provide proper positioning for the sequences to allow them to interact so the resulting amino acid sequences can properly fold. Applicant points to Pastan et al. ('599) as making a similar distinction between "spacer" and "linker" at columns 3 and 4. This has been fully considered but is not found to be persuasive, because Chaudhary et al. and Cousens et al. teach linkers that provide sufficient space to allow for proper folding, which is what the instant linkers also do. Furthermore, Pastan et al.'s ('599) teachings regarding spacers and linkers only provide more guidance to one of ordinary skill in the art to select proper linkers in the context of a circular permutin.

The rejection is deemed to be sound and is thus maintained.

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Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 15-22 drawn to an invention nonelected with traverse in Paper No. 4. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C Kemmerer

**ELIZABETH KEMMERER
PRIMARY EXAMINER**

ECK
October 12, 1999